Preparation of 2-azetidinones by cyclocondensation of carboxylic acids and imines via diphosphorustetraiodide

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General methods

All required chemicals were purchased from Merck, Fluka, and Acros chemical companies. The melting points were determined on a Buchi 535 apparatus. IR spectra were measured on a Shimadzu FT-IR 8300 spectrophotometer. NMR spectra were recorded on a Bruker spectrometer (^1H NMR 250 MHz, ^{13}C NMR 62.9 MHz) using tetramethylsilane as an internal standard and coupling constants are given in cycles per second (Hz). Elemental analyses were run on a Vario EL III elemental analyzer. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka.

General procedure for the synthesis of 2-azetidinones (**3a-j** and **5a-b**)

Diphosphorustetraiodide (0.5 mmol) was added to a solution of substituted acetic acids (1.5 mmol), imines (1.0 mmol) and triethylamine (5.0 mmol) in dry CH_2Cl_2 (20 ml) at room temperature and the mixture was stirred overnight. The reaction mixture was washed successively with saturated NaHCO_3 (15 ml) and brine (15 ml). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed to give the crude product, which was purified by crystallization from EtOAc to give pure β -lactams **3a-j** and **5a-b**.

Table 1.2-Azeidinones from imines and carboxylic acids using diphosphorustetraiodide

Entry	R ¹	R ²	R ³	<i>cis/trans</i>	Product	Yield(%)
1	4-MeOC ₆ H ₄	C ₆ H ₅	PhO	<i>cis</i>	3a	92
2	4-MeOC ₆ H ₄	C ₆ H ₅	2,4-Cl ₂ C ₆ H ₃ O	<i>cis</i>	3b	78
3	4-MeOC ₆ H ₄	C ₆ H ₅	4-ClC ₆ H ₄ O	<i>cis</i>	3c	91
4	4-MeOC ₆ H ₄	C ₆ H ₅	MeO	<i>cis</i>	3d	80
5	4-MeOC ₆ H ₄	C ₆ H ₅	PhthN	<i>trans</i>	3e	85
6	4-ClC ₆ H ₄	(NMe ₂)C ₆ H ₄ -4	PhO	<i>cis</i>	3f	88
7	4-ClC ₆ H ₄	(NMe ₂)C ₆ H ₄ -4	2,4-Cl ₂ C ₆ H ₃ O	<i>cis</i>	3g	85
8	4-ClC ₆ H ₄	(NMe ₂)C ₆ H ₄ -4	4-ClC ₆ H ₄ O	<i>cis</i>	3h	90
9	4-ClC ₆ H ₄	(NMe ₂)C ₆ H ₄ -4	MeO	<i>cis</i>	3i	81

Characterization data for new compounds and references for known compounds**1-(4-Methoxyphenyl)-3-phenoxy-4-phenylazetidin-2-one (3a)¹**

White solid.m.p: 188-189 °C. (lit. 186-188 °C).

3-(2,4-Dichlorophenoxy)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (3b)²

White solid.m.p: 150-152 °C. (lit. 148-150 °C).

3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (3c)

White solid.m.p: 177-179 °C. IR (KBr) cm⁻¹: 1749 (CO, β-lactam). ¹H NMR δ 3.79 (MeO, s, 3H), 5.35 (H-4, d, 1H, *J* = 4.4), 5.61 (H-3, d, 1H, *J* = 4.4), 6.86-7.28 (ArH, m, 13H); ¹³C NMR δ 56.0 (MeO), 63.0 (C-4), 80.6 (C-3), 114.4-156.3 (aromatic carbons), 163.0 (CO, β-lactam); Anal. Calcd for C₂₂H₁₈ClNO₃: C, 69.57; H, 4.78; N, 3.69. Found: C, 69.70; H, 4.86; N, 3.74.

3-Methoxy-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (3d)³

White solid.m.p: 166-167 °C. (lit. 165-166 °C).

2-(1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)isoindoline-1,3-dione (3e)⁴

White solid.m.p: 162-164 °C. (lit. 168°C).

1-(4-Chlorophenyl)-4-(4-(dimethylamino)phenyl)-3-phenoxyazetidin-2-one (3f)

White solid.m.p: 213-215 °C. IR (KBr) cm⁻¹: 1751 (CO, β-lactam). ¹H NMR δ 2.93 (NMe₂, s, 6H), 5.31 (H-4, d, 1H, *J* = 5), 5.65 (H-3, d, 1H, *J* = 5), 6.64-7.37 (ArH, m, 13H); ¹³C NMR δ 41.9 (NMe₂), 62.5 (C-4), 80.8 (C-3), 113.8-157.9 (aromatic carbons), 163.1 (CO, β-lactam); Anal. Calcd for C₂₃H₂₁ClN₂O₂: C, 70.31; H, 5.39; N, 7.13. Found: C, 70.42; H, 5.46; N, 7.05.

1-(4-Chlorophenyl)-3-(2,4-dichlorophenoxy)-4-(4-(dimethylamino)phenyl) azetidin-2-one (3g)

Pale-umber solid.m.p: 162-164 °C. IR (KBr) cm^{-1} : 1739 (CO, β -lactam). ^1H NMR δ 2.93 (NMe₂, s, 6H), 5.34 (H-4, d, 1H, $J = 4.5$), 5.65 (H-3, d, 1H, $J = 4.5$), 6.64-7.39 (ArH, m, 11H); ^{13}C NMR δ 42.1 (NMe₂), 62.2 (C-4), 80.9 (C-3), 112.8-152.2 (aromatic carbons), 163.2 (CO, β -lactam); Anal. Calcd for C₂₃H₁₉Cl₃N₂O₂: C, 59.82; H, 4.15; N, 6.07. Found: C, 59.90; H, 4.22; N, 6.13.

3-(4-Chlorophenoxy)-1-(4-chlorophenyl)-4-(4-(dimethylamino)phenyl)-azetidin-2-one (3h)

White solid.m.p: 206-208 °C. IR (KBr) cm^{-1} : 1748 (CO, β -lactam). ^1H NMR δ 2.94 (NMe₂, s, 6H), 5.31 (H-4, d, 1H, $J = 4.6$), 5.60 (H-3, d, 1H, $J = 4.6$), 6.63-7.38 (ArH, m, 12H); ^{13}C NMR δ 40.9 (NMe₂), 63.0 (C-4), 81.0 (C-3), 114.1-156.6 (aromatic carbons), 162.9 (CO, β -lactam); Anal. Calcd for C₂₃H₂₀Cl₂N₂O₂: C, 64.65; H, 4.72; N, 6.56. Found: C, 64.73; H, 4.78; N, 6.47.

1-(4-Chlorophenyl)-4-(4-(dimethylamino)phenyl)-3-methoxyazetidin-2-one (3i)

White solid.m.p: 163-165 °C. IR (KBr) cm^{-1} : 1742 (CO, β -lactam). ^1H NMR δ 2.91 (NMe₂, s, 6H), 3.41 (MeO, s, 3H), 5.05 (H-4, d, 1H, $J = 5$), 5.26 (H-3, d, 1H, $J = 5$), 6.60-7.31 (ArH, m, 8H); ^{13}C NMR δ 41.3 (NMe₂), 57.9 (MeO), 63.1 (C-4), 83.9 (C-3), 113.1-150.5 (aromatic carbons), 164.0 (CO, β -lactam); Anal. Calcd for C₁₈H₁₉ClN₂O₂: C, 65.35; H, 5.79; N, 8.47. Found: C, 65.44; H, 5.91; N, 8.55.

2-(1-(4-Chlorophenyl)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-3-yl) isoindoline-1,3-dione (3j)

White solid.m.p: 177-179 °C. IR (KBr) cm^{-1} : 1735, 1771 (CO, Phth), 1784 (CO, β -lactam). ^1H NMR δ 2.91 (NMe₂, s, 6H), 5.46 (H-4, d, 1H, $J = 2.5$), 5.55 (H-3, d, 1H, $J = 2.5$), 6.76-7.83 (ArH, m, 12H); ^{13}C NMR δ 42.5 (NMe₂), 60.7 (C-4), 62.0 (C-3), 112.2-151.8 (aromatic carbons), 166.0 (CO, Phth), 167.6 (CO, β -lactam); Anal. Calcd for C₂₅H₂₀ClN₃O₃: C, 67.34; H, 4.52; N, 9.42. Found: C, 67.46; H, 4.49; N, 9.48.

1-(4-Methoxyphenyl)-4-phenylspiro[azetidine-3,9'-xanthen]-2-one (5a)

Pale-umber solid.m.p: 236-238 °C. IR (KBr) cm^{-1} : 1745 (CO, β -lactam). ^1H NMR δ 3.80 (MeO, s, 3H), 5.76 (H-4, s, 1H), 6.84-7.24 (ArH, m, 17H); ^{13}C NMR δ 56.8 (MeO), 63.0 (C-4), 70.4 (C-3), 114.8-156.3 (aromatic carbons), 167.1 (CO, β -lactam); Anal.Calcd for $\text{C}_{28}\text{H}_{21}\text{NO}_3$: C, 80.17; H, 5.05; N, 3.34. Found: C, 80.28; H, 5.14; N, 3.38.

1-(4-Chlorophenyl)-2-(4-(dimethylamino)phenyl)spiro[azetidine-3,9'-xanthen]-4-one (5b)

White solid.m.p: 191-193 °C. IR (KBr) cm^{-1} : 1757 (CO, β -lactam). ^1H NMR δ 2.89 (NMe₂, s, 6H), 5.69 (H-4, s, 1H), 6.69-7.35 (ArH, m, 16H); ^{13}C NMR δ 41.2 (NMe₂), 63.4 (C-4), 70.1 (C-3), 113.1-153.0 (aromatic carbons), 167.4 (CO, β -lactam); Anal.Calcd for $\text{C}_{29}\text{H}_{23}\text{ClN}_2\text{O}_2$: C, 74.59; H, 4.96; N, 6.00. Found: C, 74.72; H, 5.08; N, 5.95.

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¹³C NMR 3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (3c)

¹H NMR 1-(4-Chlorophenyl)-4-(4-(dimethylamino)phenyl)-3-phenoxyazetidin-2-one(3f)

¹³C NMR 1-(4-Chlorophenyl)-3-(2,4-dichlorophenoxy)-4-(4-(dimethylamino)phenyl) azetidin-2-one(3g)

¹H NMR 3-(4-Chlorophenoxy)-1-(4-chlorophenyl)-4-(4-(dimethylamino)phenyl)-azetidin-2-one(3h)

¹³C NMR 3-(4-Chlorophenoxy)-1-(4-chlorophenyl)-4-(4-(dimethylamino)phenyl)-azetidin-2-one(3h)

¹H NMR 1-(4-Chlorophenyl)-4-(4-(dimethylamino)phenyl)-3-methoxyazetidin-2-one(3i)

¹³C NMR 1-(4-Chlorophenyl)-4-(4-(dimethylamino)phenyl)-3-methoxyazetidin-2-one(3i)

¹H NMR 2-(1-(4-Chlorophenyl)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-3-yl) isoindoline-1,3-dione (3j)

¹³C NMR 2-(1-(4-Chlorophenyl)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-3-yl) isoindoline-1,3-dione (3j)

¹H NMR 1-(4-Chlorophenyl)-2-(4-(dimethylamino)phenyl)spiro[azetidine-3,9'-xanthen]-4-one (5a)

¹³C NMR 1-(4-Chlorophenyl)-2-(4-(dimethylamino)phenyl)spiro[azetidine-3,9'-xanthen]-4-one (5a)

¹H NMR 1-(4-Methoxyphenyl)-4-phenylspiro[azetidine-3,9'-xanthen]-2-one (5b)

¹³C NMR 1-(4-Methoxyphenyl)-4-phenylspiro[azetidine-3,9'-xanthen]-2-one(5b)